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(71) Applicants
Imperial Chemical
Industries PLC,
(United Kingdom),
Imperial Chemical House,
Millbank,
London SW1P 3JF
(72) Inventors
Dr William George
Rathmell
Dr Anthony Michael
Skidmore
Dr Margaret Claire
Shephard
Dr Brian Conrad Baldwin
(74) Agent and/or
Address for Service
Henry Giveen Hamilton
Alner,
Imperial Chemical
Industries PLC,
Legal Dept.
Patents,
Thames House North,
Millbank,
London SW1P 4QG

(54) **Fungicidal compositions**

(57) Fungicidal compositions displaying "resistance breaking" effects and/or synergy, and having broader spectra of activity, comprise a fungicide (or co-fungitoxicant) which inhibits adenosine deaminase or blocks sterol biosynthesis in fungi and a further fungicide having a different mode of action.

GB 2 110 934 A

SPECIFICATION

Fungicidal compositions

This invention relates to compositions for combating plant fungi. More particularly the invention relates to mixtures of fungicidal substances containing a first fungicide which is either an inhibitor of adenosine deaminase or of sterol biosynthesis in fungi and at least one other anti-fungal substance having a different mode of anti-fungal effect.

It is known that plant fungi, especially races (strains, types) thereof, can develop resistance to, that is become insensitive to, anti-fungal chemicals thereby reducing the efficacy of a particular chemical. Indeed there are believed to be in existence certain plant fungal pathogens which are resistant to fungicides of the type which combat them, for example, by inhibiting their ability to biosynthesise certain steroids essential to their metabolism, for example ergosterol. These fungicides, more specifically either block the incorporation of acetate into ergosterol an essential metabolic pathway of the fungus, thereby disrupting the synthesis and function of cell membranes by the fungus. Plant pathogens of the latter type include, in particular, races etc., of powdery mildew diseases such as *Erysiphe graminis* which infect cereal plants, for example crops of barley and wheat, and mildews which infect non-cereal crops such as vines and apples, such latter diseases being, for example, *Uncinula necator, Podosphaera leucotricha* and *Sphaerotheca fuliginea* or other diseases such as *Venturia inacquatis* on apples or *Cercospora* leaf spots on peanuts, banana and sugar beet.

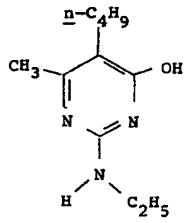
It has now been found that certain mixtures of, or combinations of, fungicides are not only less prone than the individual components thereof to suffer from reduction in their efficacy due to resistant (insensitive) species of plant pathogens infecting crops upon which they are sprayed (or the seed pre-treated with them), but in addition often display synergism, that is to say the combined antifungal effect of the mixture is greater than that which would have been expected if the fungicidal components were acting separately. Such mixtures are ones in which a pyrimidine fungicide or a sterol biosynthesis inhibiting fungicide is combined with one or more fungicides having a different mode of action against the fungal pathogens being combated.

According to the present invention there is provided an anti-fungal composition comprising either, as a first ingredient, a co-fungitoxicant or a fungicide which inhibits adenosine deaminase or a fungicide having a sterol biosynthesis blocking mode of action in its anti-fungal effect, and at least one further fungicide having a different mode of action in combating fungi.

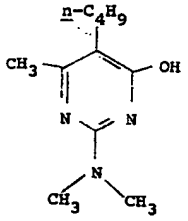
The fungicide which inhibits adenosine deaminase in fungi may be a pyrimidine fungicide and by "a pyrimidine fungicide" is intended single ring compounds such as ethirimol, dimethirimol and bupirimate. The term is not intended to embrace bicyclic and tricyclic compounds in which a central carbon atom bears a pyrimidine ring and one or more other aryl or heterocyclic rings.

The co-fungitoxicant need have no fungicidal activity in its own right; or have activity only against triazole resistant strains of a pathogen.

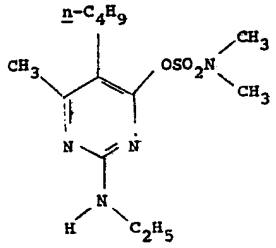
The fungicidal ethirimol is the subject of British Patent No. 1182584 and it has the chemical structure:–



The fungicide dimethirimol is also the subject of British Patent No. 1182584 and it has the chemical structure:–



The fungicide bupirimate is the subject of British Patent No. 1400710 and it has the chemical structure:–



The foregoing fungicides are, as already stated, considered to have an anti-fungal effect by inhibition of the action of adenosine deaminase in the meta-

Certain of the /The Chemical/mathematical formula(e) appearing in the printed specification was/were submitted after the date of filing, the formula(e) originally submitted being incapable of being satisfactorily reproduced.

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bolism of fungi.

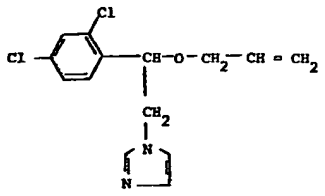
In a further aspect, therefore, the invention provides an anti-fungal composition comprising a fungicide which is ethirimol, dimethirimol or bupirimate or an anti-fungal substance which is an inhibitor of the ability of the fungus to biosynthesise sterols and at least one further fungicide which has a different mode of action in combating fungi. Examples of fungicidal substances having the capacity to inhibit sterol biosynthesis and the classes to which the belong, are as follows:–

Table A

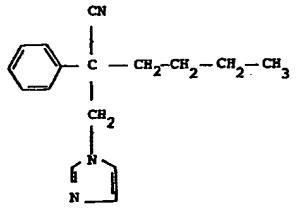
CLASS AND COMMON NAME OF FUNGICIDE	TRADE NAMES OF FUNGICIDAL PRODUCTS CONTAINING THE FUNGICIDE
Imidazoles	
Imazalil	Fungaflor, present in Mist-O-Matic Murbenine Plus, Mist-O-Matic Muridal Seed Treatment
Prochloraz	Sportak
Fenaponil	–
Piperazines	
Triforine	Saprol, Triforine LST, present in Nimrod T
Pyridines	
Buthiobate	Parnon
EL 241	–
Piperidines	
Fenpropidin	–
Pyrimidines	
Fenarimol	Rubigan
Nuarimol	Triminol, present in Mist-O-Matic Murox Seed Treatment
Triarimol	–
Triazoles	
Bitertanol	–
Diclobutrazol	Vigil, present in Vigil K, present in Vigil T
Fluotrimazole	Persulon
Propiconazole	Tilt 250 EC, in Tilt mbc 45WP
Triadimefon	Bayleton, Bayleton 5, in Bayleton, BM, Bayleton CF
Triadimenol	Baytan
Etaconazole	Vanguard, Sonax
PP969	–
Morpholines	
Dodemorph	BASF F238
Fenpropimorph	Corbel, Mistral
Tridemorph	Calixin, Bardew, Beacon, Cosmic

The chemical structures of the foregoing chemical substances are set out below:–

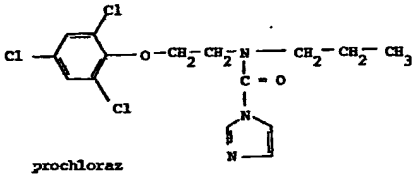
IMIDAZOLES



imazalil

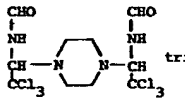


fenaponil



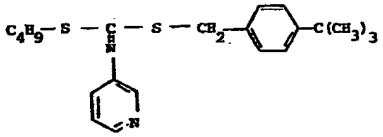
prochloraz

PIPERAZINES

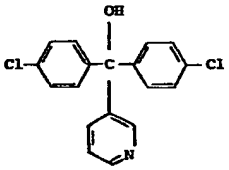


triforine

PYRIDINES



buthiobate



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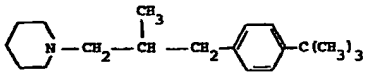
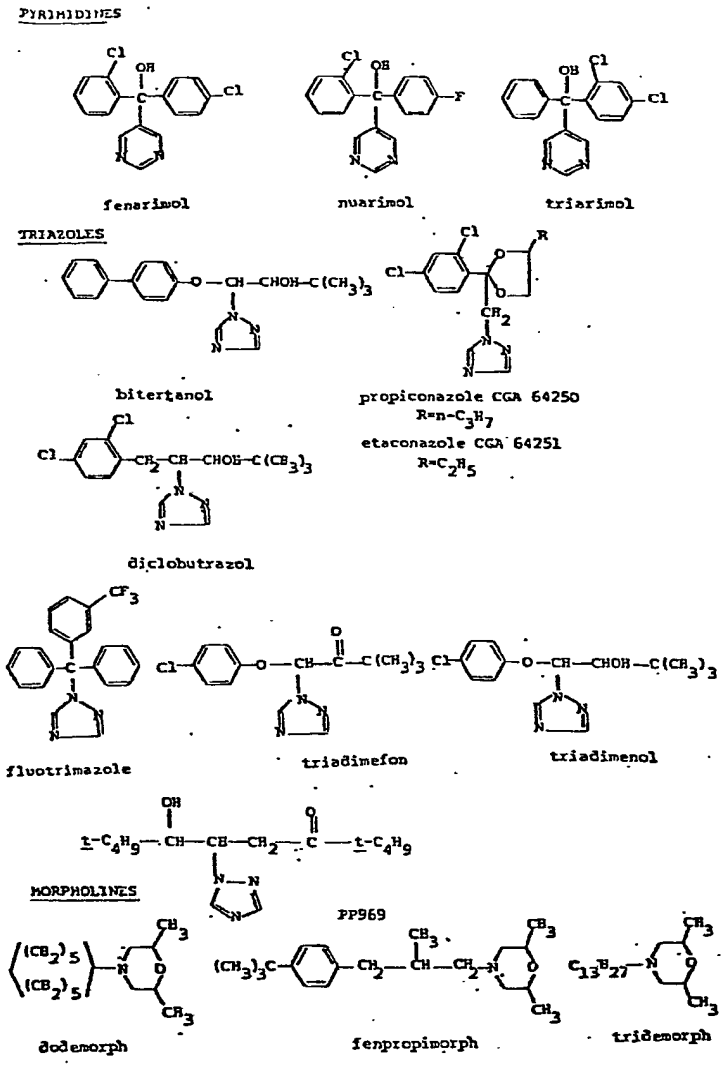
PIPERIDINES



fenpropidin



In a further aspect, therefore, the invention provides a fungicidal composition comprising, as active ingredients, a first fungicide which is either ethirimol, dimethirimol or bupirimate or which is an inhibitor of the ability of a plant fungus to biosynthesise sterols and is a specific fungicidal substance from the foregoing list of chemical compounds, and at least one further fungicidal substance having a mode of action in combating fungi which is different from that of the first fungicide.

As far as suitable further fungicidal substances are concerned these may be any general, i.e. metabolic, inhibitor of plant fungal growth, for example a respiratory inhibitor.

By the term "general metabolic inhibiting agent" (including respiratory inhibitors) are intended fungicidal and anti-fungal substances such as those listed below under chemical class headings with examples of specific fungicides listed and an indication of their believed mode of action.

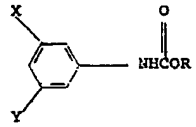
Table B

1. Site specific inhibitors

Acylalanies	–furalaxyl, metalaxyl, ofurace, galben.
Mode of action	–?
Antibiotics	–cycloheximide etc.
Mode of action	–inhibits protein synthesis
Benzimidazoles	–benomyl, carbendazim, thiophanate methyl, thiabendazole, fuberidazole
Mode of action	–inhibition of mitosis
Carboxamides	–carboxin, oxycarboxin, methfuroxam, fenfuram, furmecyclox, benodanil, pyracarbolid
Mode of action	–interference with respiration by blocking succinate dehydrogenase
Dicarboxamides	–iprodione, procymidon, vinclozolin, M8164 (Serinal)
Mode of action	–interference with mitotic segregation
Aromatic hydrocarbons	–2-phenylphenol, sodium -o-phenyl-phenate biphenyl, chloroneb, dichloran, quintozene, tecnazene.
Mode of action	–interference with mitotic segregation
Dinitrophenols	–dinapacryl, dinocap
Mode of action	–uncouplers of oxidative phosphorylation
Dimethyldithio-carbamates	–thiram
Mode of action	–inhibitors of pyruvate dehydrogenation
Guanidines	–dodine, guazatine
Mode of action	–affect cell membrane permeability
Organotin compounds	–fentin
Mode of action	–inhibition of oxidative phosphorylation
Organic phosphates and isoprothiolane	–pyrazophos, edinfenphos, BP, –isoprothiolane
Mode of action	–inhibition of the conversion of phosphatidyl-ethanolamine to phosphatidyl-choline
Acetamides	–curzate
Mode of action	–unknown
Aminobutane	–2-aminobutane
Mode of action	–inhibition of pyruvic dehydrogenase
Anthraquinones	–dithianon
Mode of action	–inhibition of glycolysis
Isoxazolones	–drazoxalon
Mode of action	–uncoupler of respiration
Nitroisophthalates	–nitrothal-isopropyl
Mode of action	–unknown
Organic phosphates	–ditalimfos
Mode of action	–disrupts metabolism
Quinoxalines	–quinomethionate
Mode of action	–?
Sulphamides	–dichlofluanid, tolyfluanid
Mode of action	–?
Thiocarbamates	–prothiocarb, propanocarb
Mode of action	–causes cell membrane disfunction

N-Phenylcarbamate derivatives

Such as those disclosed in European Patent Application No. 81109561.1 (Publication No. 51871) having the general formula:



where X and Y are alkyl, alkoxy or halogen and R is methol or ethyl.

Table C

Thiadiazoles	–etridazole
Mode of action	–interferes with respiration
2. Multisite inhibitors	
Dithiocarbamates	–maneb, zineb, mancozeb, nabam, propineb etc.
Mode of ation	–inhibitors of thiol groups
Phthalimides	–captafol, captan, folpet
Mode of action	–inhibitors of thiol groups
Phthalonitriles	–chlorothanlonil
Mode of action	–inhibitor of thiol groups
Copper compounds	–various
Mode of action	–?
Mercury compounds	–various
Mode of action	–?
Sulphur	–
Mode of action	–?
Aluminium compounds	–FOSETYL ALUMINIUM
Mode of action	–?

Anionic agents

Sodium dodecylbenzene sulphonate
Sodium dodecylsulphate
Sodium C13/C15 alcohol ether sulphonate
Sodium ceto stearyl phosphate ester
Dioctyl sodium sulphosuccinate
Sodium isopropyl naphthalene sulphonate
Sodium methylene bis naphthalene sulphonate

Cationic agents

Cetyl trimethyl ammonium chloride
Salts of long chain primary, secondary or tertiary amine
Alkyl propylene amines
Lauryl pyridinium bromide
Quaternised fatty amine ethoxylate
Alkyldimethyl benzyl ammonium chloride
1 - Hydroxyethyl - 2 - alkyl imidazoline.

In a further aspect, therefore, the invention provides a fungicidal composition comprising, as active ingredients, a first fungicide which is either ethirimol, dimethirimol or bupirimate or which is an inhibitor of the ability of a plant fungus to biosynthesise sterols and is a specific fungicidal substance from the foregoing list of chemical compounds, and at least one further fungicidal substance having a mode of action in combating fungi which is different from that of the first fungicide and which is a substance chosen from the specific fungicidal substances recited in the immediately preceding list.

The invention also provides a process for treating seed which comprises dressing seed with a composition according to the invention.

In another aspect seed may be dressed first with ethirimol, or with a fungicide which inhibits sterol biosynthesis in plant fungi and then with a further fungicide as defined above. Batches of seed treated separately with a first fungicide and with a further fungicidal substance may be mixed wth untreated seed, e.g. tumbled therewith, so as to produce a

batch of treated seed.

The invention further provides, in yet another aspect, a process for combating plant fungi which comprises applying to a plant, to seed of a plant, or to the locus of a plant or seed, an anti-fungal composition as defined in any of the preceding paragraphs.

In a still further aspect the invention provides a process of combating plant fungi which comprises alternately treating, e.g. spraying, crops with ethirimol, dimethirimol or bupirimate, or with a fungicide which inhibits sterol biosynthesis in plant fungi, and then with a further fungicidal substance as defined above.

The amounts of fungicidal substance used in the invention compositions can readily be determined by simple experimentation, but in general, in view of the ability to counter resistant (insensitive) races etc., of fungi and/or the synergism displayed, it is not necessary to use the full rates of chemical normally applied.

EXAMPLE 1

A series of initial experiments were carried out to determine the efficacy of a range of co-fungitoxicants in controlling two isolates of *E. graminis* f.sp *hordei* in the absence of triadimefon with the following results (Table 1).

Sumisclex showed activity against one or both fungus isolates whereas Sanspor and Terrazole were inactive.

Sumisclex was further tested to determine in more detail its rate response against the two isolates of *E graminis* f.sp *hordei* (Table 2). Based on these data, suboptimal rates of this compound were chosen for a further interaction experiment involving triadimefon (Tables 3 and 4).

Against both isolates the addition of Sumisclex at 150 ppm to triadimefon at 0.1 ppm boosted the activity of triadimefon in the degree of disease control achieved. The margin of this increase in activity must be accounted for by a synergistic interaction between the two compounds.

Materials and Methods

1. *Plant Sowing*: Approximately 10 seeds/pot of Golden Promise spring barley were sown into John Innes compost number one in minipots.

1.1 *Growth Conditions*: Day temperature 21°C, Relative Humidity 60%, Night temeprature 17°C, Relative Humidity 95%, 16 hours daylength. The plants were watered by an automatic watering system.

2. *Test Method for spraying the plants*: Plants were sprayed at 6 days old; the chemicals under test were made up in 0.03% Tween 20; and the plants were sprayed to give an even coverage on both leaf surfaces, using a hand-held De Vilbiss spray gun at 15 psi (pounds per square inch).

After spraying, the plants were transferred to a second growth chamber for 24 hours to allow plants to dry.

2.1 *Growth Conditions in this room were*: Day temperature 24°C, Relative Humidity 60%, Night temperature 17°C, Relative Humidity 95%, 16 hours daylength. The plants were watered by an automatic watering system.

3. *Method for preparing the repli dishes*: Plants were removed from the Growth Room and cut into 2 cm lengths from just below the tip of the prophyll. Only uniform plants were chosen. Only one leaf piece was taken from each prophyll. The cut leaf pieces were then placed into a slit in the agar in the repli dish. (the dishes contained 45 ml of 10% Tap water agar), the top rate of chemical first proceeded by lower rate. For each chemical rate there were 5 replicate leaf pieces.

When changing from one rate of chemical to a lower rate the scissors and forceps were wiped with a swab soaked in Methanol to avoid contamination. Particular attention was paid to ensure that the leaf pieces did not touch the lid nor overlap one another in the dish. The former would cause condensation to run down the leaf pieces and could wash off some spores, the latter would lead to uneven inoculation and hence misleading results.

4. *Inoculation Method*: Infected leaf pieces were cut from stock plants in propagating tubes and placed in petri dishes on moist foam squares 48 hours prior to inoculation. The infected leaf pieces were kept in a 19°C constant temperature room with a 16 hour day length.

Repli dishes were inoculated using a settling tower, the tower was placed over the opened repli dish and sporulating leaf pieces held in forceps were placed in the nose of the tower. An air line set at 3/4 lb per square inch pressure was used to blow the spores off the leaf pieces and into the settling tower.

The repli dishes remained inside the tower for 2 minutes after which the tower was removed and the lid replaced on the repli dish. The tower, forceps and air lines were swabbed with Methanol to decontaminate them.

Once all the repli dishes were inoculated they were placed in a 19°C constant temperature room with a 16 hour daylength where they remained until assessment 6 days later.

5. *Assessment*: Percentage sporulating disease was assessed on each leaf piece.

TABLE 1
Disease Control

Fungitoxicant	Rate ppm ai.	*Erysiphe graminis* f.sp *hordei* isolate 1	2
Sumisclex (procymidone)	500	99	100
	250	98	100
	125	65	39
	100	93	56
	50	98	25
	0	0	0

TABLE 2
2 % Disease Control

Fungitoxicant	Rate ppm ai.	*Erysiphe graminis* f.sp *hordei* isolate 1	2
Sumisclex (procymidone)	250	99	87
	200	96	30
	175	97	69
	150	27	57
	125	22	27
	0	0	0

TABLE 3
Isolate 1 % Disease Control

	Triadimefon Rage ppm ai	Triadimefon + 150 ppm Sumisclex
	0.25	–
	0.1	59 (20)
	0.05	30
	0.025	43
	0.01	–
Sumisclex	150	0
Untreated	–	0
Actual untreated disease level	74%	

( ) = Activity of triadimefon alone in same test dish at 0.1 ppm.

TABLE 4
Isolate 2 % Disease Control

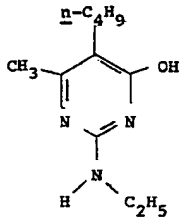
	Triadimefon Rate ppm ai	Triadimefon + 150 ppm Sumisclex
	0.5	93 (52)
	0.25	0
	0.1	–15
	0.05	
Sumisclex	150	–31
Untreated	–	0
Actual Untreated Disease level		61%

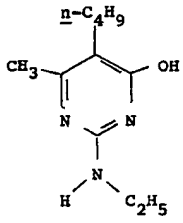
( ) = Activity of triadimefon in same test dish at 0.1 ppm.

CLAIMS

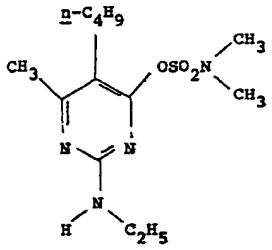
1. An anti-fungal composition comprising as a first ingredient either a co-fungitoxicant or a fungicide which inhibits adenosine deaminase or a fungicide having a sterol biosynthesis blocking mode of action in its anti-fungal effect, and at least one further fungicide having a different mode of action in combating fungi.

2. An anti-fungal composition according to claim 1 comprising a adenosine deaminase inhibitor which is a pyrimidine derivative having the structure:





or



3. An anti-fungal composition according to claim 1 comprising a fungicide having a sterol biosynthesis blocking mode of action and which is an imidazole, piperazine, pyridine, piperidine, pyrimidine, triazole or morpholine derivative as hereinbefore defined.

4. An anti-fungal composition according to any of the preceding claims wherein the further fungicide is a site specific inhibitor or multisite inhibitor, as hereinbefore defined, or a general, eg. metabolic, inhibitor of fungal growth.

5. An anti-fungal composition according to any of the preceding claims wherein the further fungicide comprises any of the specific fungicidal substances defined hereinbefore.

6. A process for treating seed which comprises dressing seed with a composition according to the invention.

7. A process for dressing seed wherein seed is dressed first with ethirimol, or with a fungicide which inhibits sterol biosynthesis in plant fungi, and then with a further fungicide as defined in any of the preceding claims.

8. A process for combating plant fungi which comprises applying to a plant, to seed of a plant, or to the locus of a plant or seed, an anti-fungal composition as defined in any of the proceeding claims.

9. A process of combating plant fungi which comprises alternately treating, eg. spraying, crops with ethirimol, dimethirimol or bupirimate, or with a fungicide which inhibits sterol biosynthesis in plant fungi, and then with a further fungicidal substance as defined above.

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